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(54) AMINOPHTHALAZINES AND PHARMACEUTICAL COMPOSITIONS THEREOF

(71) We, ASPRO - NICHOLAS LIMITED, a British company, of 16 Berkley Street, London W.1., England, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to pharmacologically active phthalazines, to a method for their preparation, to pharmaceutical compositions containing them and to a method of treatment involving their use.

The phthalazines of the present invention are represented by the formula:—

I

and an acid addition salts and quaternary ammonium derivatives thereof wherein

R represents aryl or aralkyl;

R_1 and R_2, which may be the same or different, represent hydrogen; cycloalkyl; or cycloalkyl-alkyl; provided that both R_1 and R_2 are not hydrogen; or

R_1 and R_2 separately represent the same or different heterocyclic or heterocyclic-alkyl or, together with the adjacent nitrogen, represent heterocyclic, the said heterocyclic groups being rings of 5 to 7 atoms at least one of which atoms is carbon, and at least one and optionally up to four of which atoms are hetero atoms selected from nitrogen, oxygen and sulphur; and

R_3 and R_4, which may be the same or different, represent hydrogen; halogen; cyano; hydroxy; nitro; amino; alkylamino; carboxy; carboxyamino; alkyl; alkylcarbonyl; alkoxy; alkoxycarbonyl; hydroxy alkyl; halogenoalkyl; or alkyl- or aryl-thio, -sulphinyl or -sulphonyl.

The aforementioned heterocyclic rings may be unsubstituted or substituted by alkyl; hydroxyalkyl; halogenoalkyl; aryl; aralkyl; carboxyalkyl; alkoxy- or aralkoxy-alkyl; alkoxy- or aralkoxy-carbonyl; alkoxy- or aralkoxy-carbonalkyl; alkyl- or aryl-sulphonyloxyalkyl; aminoalkyl; alkylamino-alkyl; acyl; acyl- or acyloxy-alkyl; or by a further heterocyclic or heterocyclic-alkyl group, the heterocyclic rings of which have 5 to 7 atoms, one or two of which are heteroatoms selected from nitrogen, oxygen or sulphur and the remainder of which ring atoms are carbon, which rings are themselves optionally substituted by alkyl, hydroxyalkyl or halogenoalkyl.

By "aryl" as used herein we mean to include phenyl and phenyl substituted by one or more of the same or different halogen; cyano; hydroxy; nitro; amino; alkylamino; carboxy; carboxyamido; alkyl; alkylcarbonyl; alkoxy; alkoxycarbonyl; hydroxyalkyl; halogenoalkyl; or alkyl-, phenyl- or alkyl-phenyl-thio, -sulphinyl or -sulphonyl.

By "alkyl" as used herein whether

explicitly (except in the term cycloalkyl) or implicitly as in, for example, acyl (i.e. alkylcarbonyl), we mean to include straight and branched chain radicals of up to 12 carbons which are saturated or unsaturated by one or more double or triple bonds.

Examples of suitable heterocyclic and heterocyclicalkyl and, subject to the restrictions in the definition above, heterocyclic-substituted heterocyclic radicals are imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, picolyl, pyridylethyl, homopiperidyl, thiazolinyl, thiazolyl, homopiperazinyl, homomorpholinyl, piperazinyl, morpholinyl, morpholinylpropyl, thiazinyl, thiazolidinyl, pyrrolyl, imidazolyl, pyrazolyl, pyrrolidinyl, piperidinyl, pyrrolinyl, piperidylmethyl, morpholinylethyl, 4 - methylpiperazinyl, 2 - phenylpiperidyl, 3 - aminomethylpyrrolidinyl, 3 - chloroethylpiperidyl, 3 - hydroxypyrrolidinyl, 2 - methoxyethylmorpholinyl, 4 - phenylpiperazinyl, *o* - tolylpiperazinyl, triazolyl, tetrazolyl, oxadiazolyl, thienyl, hydroxyethylpiperazinyl, acetoxyethylpiperazinyl, 4 - picolylpiperazinyl, methylsulphonyloxyethylpyrazolinyl and piperidinylpropylpiperidinyl.

Examples of suitable aryl and aralkyl radicals include phenyl, tolyl, xylyl, cumenyl, 2,3 - dimethoxyphenyl, chlorophenyl, 2,4 - dibromophenyl, cyanophenyl, hydroxyphenyl, methylthiophenyl, 4 - (*o* - tolylsulphinyl)-phenyl, benzyl, styryl, phenethyl, 2,3 - xylylmethyl, 3 - ethylsulphonylphenyl, 2,4 - dimethoxybenzyl, 2,3,6 - trichlorobenzyl, γ - phenylpropyl, 4 - (*o* - tolyl)butyl, 2 - (2′,4′ - dimethoxyphenyl) ether, 1 - methyl - 2 - phenylethyl, 3 - fluorophenylalkyl, 2 - methyl - 3 - phenylpropyl, 3 - phenylprop - 2 - ynyl, 2 - chloro - 3,5 - dimethylphenyl and 2 - benzylbut - 1 - enyl.

Examples of suitable alkyl radicals are methyl, ethyl, propyl, butyl, amyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, ethenyl, ethynyl, prop - 1 - enyl, prop - 2 - enyl, (i.e. allyl), prop - 1 - ynyl, prop - 2 - ynyl (i.e. propargyl), but - 1 - enyl, but - 1 - ynyl, but - 2 - enyl, but - 2 - ynyl, but - 3 - enyl, pent - 1 - enyl, pent - 2 - enyl, pent - 2 - ynyl, pent - 4 - ynyl, 2 - methylbut - 1 - enyl, 3 - methylbut - 1 - ynyl, 2 - methylbut - 2 - enyl, and 1,1 - dimethylprop - 2 - enyl.

Examples of suitable cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

A particular preferred group of compounds of formula I are those in which

R represents phenyl or phenyl-lower alkyl (the phenyl or phenyl moiety of which is optionally substituted by halogen; cyano; hydroxy; nitro; amino; lower alkylamino; lower alkyl; lower alkylcarbonyl; lower alkoxy; lower alkoxycarbonyl; hydroxy lower alkyl; halogeno lower alkyl; or lower alkylthio, -sulphinyl or -sulphonyl);

R_3 and R_4, which may be the same or different represent hydrogen; halogen; cyano; hydroxy; nitro; amino; lower alkylomino; lower alkyl; lower alkylcarbonyl; lower alkoxy; lower alkoxycarbonyl; hydroxy lower alkyl; halogeno lower alkyl; or lower alkylthio, -sulphinyl or -sulphonyl;

R_1 represents hydrogen;

R_2 represents cycloalkyl or cycloalkyl-lower alkyl (the cycloalkyl or cycloalkyl moiety of which has 3 to 6 carbons); or heterocyclic or heterocyclic-lower alkyl; or

R_1 and R_2, together with the adjacent nitrogen, represent a heterocyclic ring; the heterocyclic rings represented by R_2, or R_1 and R_2 together, having from 5 to 6 ring atoms, at least one of which is carbon and at least one, optionally up to 4, of which atoms are heteroatoms selected from nitrogen, oxygen or sulphur, which heterocyclic rings are optionally substituted by lower alkyl; hydroxy- or halogeno-lower alkyl, phenyl; phenyl(lower) alkyl; carboxy(lower)alkyl; lower alkoxy- or phenyl(lower) alkoxy-lower alkyl; lower alkoxy-carbonyl or -carbonyl-(lower) alkyl; lower alkyl- or phenylsulphonyloxy(lower)alkyl; amino(lower)alkyl; lower alkylamino(lower)alkyl; lower acyl; lower acyl- or lower acyloxy-lower alkyl; or by a further heterocyclic or heterocyclic-lower alkyl group, the further heterocyclic rings having from 5 to 6 ring atoms, one or two of which are heteroatoms selected from nitrogen, oxygen or sulphur and the remainder of which ring atoms are carbon, which further rings are optionally substituted by lower alkyl, hydroxy- or halogeno-lower alkyl, the phenyl substitutents or the phenyl moiety of substituents on the aforementioned heterocyclic rings being optionally substituted by halogen, cyano, hydroxy, amino, lower alkylamino, lower alkyl or lower alkoxy.

Within the aforementioned preferred group of compounds, particularly useful pharmacological properties are to be found in compounds of formula I in which R_3 and R_4, which may be the same or different, represent hydrogen or halogen;

R represnts phenyl or benzyl, the phenyl or phenyl moiety of which is optionally substituted by halogen, cyano, hydroxy, amino, alkylamino, alkyl, alkoxy or alkylthio (the alkyl or alkoxy moieties of which groups have 1 to 4 carbons); and either

R_1 represents hydrogen and R_2 represents cycloalkyl of 3 to 6 carbon heterocyclic or heterocyclic-lower alkyl, or

R_1 and R_2, together with the adjacent nitrogen, represent a heterocyclic ring;

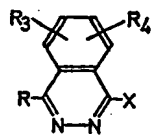
the heterocyclic rings of R_2, or R_1 and R_2 together, having from 5 to 6 ring atoms up to two of which are nitrogen, up to one of which is oxygen, and the remainder of

which are carbon, which heterocyclic rings are optionally substituted by alkyl, hydroxyalkyl or halogenoalkyl of 1 to 4 carbons; phenyl or benzyl; methoxy- or ethoxycarbonyl, -carbonylmethyl or -carbonyl ethyl; acetyl, or propionyl; acetyl-, propionyl-, acetyloxy- or propionyloxy- methyl or -ethyl; or by a further heterocyclic or heterocyclicmethyl, ethyl, propyl or butyl, the further heterocyclic rings having from 5 to 6 ring atoms, up to two of which are nitrogen, up to one of which is oxygen and the remainder of which are carbon, which further rings are optionally substituted by alkyl, hydroxyalkyl or halogenoalkyl of 1 to 4 carbons, the phenyl substitutents or the phenyl moiety of substituents on the heterocyclic rings being optionally substituted by halogen; hydroxy; methyl; ethyl; methoxy or ethoxy.

Where in this specification reference is made to a substituent without reference to its isomeric state, that substituent includes all its isomers, e.g. reference to butyl includes *n* - butyl, iso - butyl, *s* - butyl and *t*-butyl.

The term "lower" in qualifying various groups is used herein to mean those groups containing up to 6 carbon atoms.

According to a feature of the present invention, there is provided a process for preparing the phthalazines of the present invention which comprises reacting a compound of the formula:—



II

wherein R_3 and R_4 are as defined in formula I and X represents halogen, or alkyl- or aryl-thio, -sulphinyl or -sulphonyl; with an amine, or an acid salt thereof, of the formula:—

$$HNR_1R_2 \qquad III$$

wherein R_1 and R_2 are as defined in formula I.

The reaction may be carried out in the presence or absence of a solvent and normally will be carried out at elevated temperatures. When a solvent is used, the reaction is conveniently carried at the reflux temperature of the reaction mixture. Reaction times may vary for example from about 1 to 24 hours depending on the reaction conditions. When a solvent is used, suitable solvents include benzene, chloroform, toluene, acetone dioxan, dimethylformamide, and dimethylsulphoxide.

If desired, a substituent on a compound prepared according to the foregoing process may be converted to another substituent falling within the defined substituents in formula I. These conversions are carried out by methods well known *per se*. Thus, for example, a hydroxyalkyl substituent may be converted to a halogenoalkyl substitutent by reaction with a halogenating agent such as thionyl chloride, phosphorus tribromide in the presence of an inert solvent such as chloroform. An alkoxycarbonyl substituent may be converted to a hydrogen atom by the action of heat under basic conditions. A hydroxyalkyl substituent may be converted to an acyloxyalkyl substituent by action of a suitable acylating agent usually at elevated temperatures.

An unsubstituted imino group, for example in a piperazinyl group, may be alkylated or acylated using conventional means such as by reaction with an alkylating or acylating agent for example an alkyl or acyl halide. Similarly the replacement of the imino hydrogen with an alkoxycarbonylalkyl group may be accomplished by reaction with an α-halogeno alkanoic ester.

It will be clear to those skilled in the art that other substituents may likewise be converted and accordingly a feature of the process of the present invention includes the optional conversion by methods known *per se* of a substituent on the compound produced by reacting compounds of formulae II and III to another substituent falling within the definition of substituents on compounds of formula I.

The compounds produced by the foregoing process may be isolated either *per se* or as acid addition salts or quaternary ammonium derivatives thereof.

The acid addition salts are preferably the pharmaceutically acceptable, non-toxic addition salts with suitable acids, such as those with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example, glycollic, maleic, hydroxymaleic, malic, tartaric, citric, salicylic, *o* - acetyoxybenzoic, nicotinic or isonicotinic acid, or organic sulphonic acids for example methane sulphonic, ethane sulphonic, 2 - hydroxyethane sulphonic, toluene - *p* - sulphonic, or naphthalene - 2 - sulphonic acid. Apart from pharmaceutically acceptable acid addition salts, other salts are also included within the scope of acid addition salts such as, for example, those with picric or oxalic acid; they may serve as intermediates in the purification of the compounds or in the preparation of other, for example, pharmaceutically acceptable, acid addition salts, or are useful for identification, characterization or purification of the bases.

A resulting acid addition salt may be converted into the free compound according

to known methods, for example, by treating it with a base, such as with a metal hydroxide or alkoxide, for example an alkali metal or alkaline earth metal hydroxide, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide or calcium hydroxide; with a metal carbonate, such as an alkali metal or an alkaline earth metal carbonate or hydrogen carbonate, for example, sodium potassium or calcium carbonate or hydrogen carbonate; with ammonia; or with a hydroxyl ion exchange preparation, or with any other suitable reagent.

A resulting acid addition salt may also be converted into another acid addition salt according to known methods; for example, a salt with an inorganic acid may be treated with a metal salt, for example a sodium, barium or silver salt, of an acid in a suitable diluent, in which a resulting inorganic salt is insoluble and is thus removed from the reaction medium. An acid addition salt may also be converted into another acid addition salt by treatment with an anion exchange preparation.

Quarternary ammonium derivatives of the compounds of this invention are particularly those formed by reaction with lower alkyl halides, for example, methyl, ethyl, or propyl chloride, bromide or iodide; di-lower alkyl sulphates, for example, dimethyl or diethyl sulphate; lower alkyl lower alkane sulphonates, for example, methyl or ethyl methane sulphonate or ethane sulphonate; lower alkyl aryl sulphonates, for example methyl or ethyl p-toluene sulphonates; and phenyl-lower alkyl halides, for example benzyl or phenethyl chloride, bromide or iodide. Also included are the quaternary ammonium hydroxides and the quaternary ammonium compounds having as anions those of other inorganic or organic acids, for example those of the acids used for the preparation of the previously-mentioned acid addition salts.

The compounds of the present invention posses useful pharmacological properties. Such properties include anti-inflammatory activity and in particular anti-rheumatic activity. Certain of the compounds of formula I also appear to produce an immunosuppressive effect in the animal body.

In the method aspect of the invention, there is provided a method of treating inflammation in non-human animals comprising administering to said animals an amount effective to reduce inflammation of a phthalazine derivative as hereinbefore defined or an acid addition salt or quaternary ammonium derivative thereof.

In the composition aspect of the invention there are provided pharmaceutical formulations in which form the active compounds of the invention will normally be utilised. Such formulations are prepared in a manner well known in the pharmaceutical art and usually comprise at least one active compound of the invention in admixture or otherwise in association with a pharmaceutically acceptable carrier therefor. For making these formulations the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed or encapsulated in a capsule, sachet, cachet, paper or other container. A carrier or diluent may be solid semi-solid or liquid material which serves as a vehicle, excipient or medium for the active ingredient. Some examples of such diluents or carriers are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, liquid paraffin, cocoa butter, oil of theobroma, alginates, tragacanth, gelatin, syrup B.P., methyl cellulose, polyoxyethylene sorbitan monolaurate, methyl- and propyl-hydroxybenzoate, talc, magnesium stearate or mineral oil.

The formulations of the invention may be adapted for enteral or parenteral use and may be administered to a subject requiring treatment, for example an animal suffering an inflammatory condition, in the form for example tablets, capsules, suppositories, solutions or suspensions. The dosage required for the treatment of any animal will usually fall within the range of 0.01 to 250 mg/kg. For example in the treatment of adult humans, each dosage of active ingredient will normally be from 0.01 to 15 mg/Kg, whereas in the treatment of test animals such as mice and rabbits a dosage of 10 to 200 mg/Kg may be used. The formulations of the invention may therefore be provided in dosage unit form, preferably each dosage unit containing from 1 to 1000 mg., more advantageously from 5 to 500 mg., and most preferably from 10 to 250 mg. of the active ingredient of the invention.

The following Examples will further illustrate the preparation of the novel compounds of this invention:—

Example 1

1 - Chloro - 4 - phenylphthalazine (10 g.) and N - methylpiperazine (8.5 g.) in dry benzene (40 ml) were heated under reflux for 5½ hours. The solvent was evaporated off and the residue treated with water. This product was extracted with chloroform and removal of the solvent provided the crude base. On recrystallisation from benzene/light petroleum (b.p. 40—50°C), 1 - (4' - methyl - 1' - piperazinyl) - 4 - phenyl - phthalazine, m.p. 160—2°C (9.1 g. 72%) was obtained.

Example 2

1 - Chloro - 4 - phenylphthalazine (48.1 g.) and N - (2 - hydroxyethyl) piperazine (52 g.) in dry dioxan (200 ml.) were heated under reflux for 3 hours. The solvent was

evaporated off under reduced pressure and water was added to the residue. The product was extracted with chloroform, removal of the solvent gave the crude base, and recrystallisation from methanol provided crystals of 1 - [4′ - (3″ - hydroxyethyl)-piperazin - 1′ - yl] - 4 - phenylphthalazine m.p. 223—5°C (53 g. 79%).

Example 3

To N - ethoxycarbonylpiperazine (17 g.) in dry dioxan (50 ml.) was added 1 - chloro - 4 - phenyl phthalazine (12.8 g.) and the solution heated under reflux for 2 hours. The solvent was then removed under reduced pressure and the residue treated with water and extracted with chloroform. The chloroform was removed under reduced pressure and the gummy residue granulated under light petroleum (b.p. 40—60°C) to provide a crude product. Recrystallisation from isopropanol (130 ml.) gave 1 - (4′ - ethoxycarbonylpiperazin - 1′ - yl) - 4 - phenylphthalazine, m.p. 144—6°C (12.7 g., 66%).

Example 4

1 - Chloro - 4 - phenylphthalazine (16 g.) and N - aminopropyl morpholine (23 g.) in dry dioxan (65 ml.) were heated under reflux for 2½ hours. The solvent was then distilled off under reduced pressure and water was added to the residue. The product obtained via extraction with chloroform was granulated under light petroleum to give the crude amine. Recrystallisation from ethyl acetate (150 ml.) provided 1 - [(3′ - morpholino-propyl)amino] - 4 - phenyl phthalazine, m.p. 127°C (18 g., 78%).

Example 5

A solution of 1 - chloro - 4 - (*p* - chloro-phenyl)phthalazine (13.7 g.) and N - (*β* - hydroxyethyl)piperazine (13 g.) in dry dioxan (70 ml.) was heated under reflux with stirring for 3 hours. After cooling, the solution was poured into water (500 ml.) and the resulting precipitate was filtered off, washed with water, dried and recrystallised from methanol to yield 1 - (4′ - *β* - hydroxyethyl-piperazine - 1′ - yl) - 4 - (p - chloro-phenyl)phthalazine, m.p. 210—2°C. (12.2 g., 64%).

Example 6

1 - Chloro - 4 - phenylphthalazine (16 g.) and piperidine (13.5) g.) in dry dioxan (60 ml.) were heated under reflux for 2 hours. After standing overnight, the solvent was evaporated off under reduced pressure and water (600 ml.) was added to the residue. The solids were filtered off, washed well with water, and dried in a vacuum desiccator. The crude product was recrystallised from methanol to yield 1 - (piperidin - 1′ - yl) - 4 - phenylphthalazine (10.5 g. 55%) m.p. 158—9°C. A further crop (2.8 g.) m.p. 158—9°C was obtained from the mother liquors.

Example 7

By methods similar to those described above, the following compounds were prepared:—

1 - (pyrrolidin - 1′ - yl) - 4 - phenyl-phthalazine, m.p. 116—8°C (yield 55%)
1 - (4′ - *o*.tolylpiperazine - 1′ - yl) - 4 - phenylphthalazine, m.p. 204—5°C (yield 80%).
1 - [4′ - [1″ - (1‴ - *β* - hydroxyethyl-piperidin - 4‴ - yl)prop - 3″ - yl]-piperidin 1′ - yl] - 4 - phenylphthalazine, m.p. 135—7°C (yield 66%).
1 - (4′ - *β* - hydroxyethylpiperidinyl) - 4 - phenylphthalazine, m.p. 185—7°C (yield 68%).
1 - (4′ - *β* - hydroxyethylpiperazin - 1′ - yl) - 4 - benzylphthalazine, m.p. 145—6°C
1 - (4′ - acetylmethylpiperazin - 1′ - yl) - 4 - phenylphthalazine, m.p. 162—4°C.
1 - (4′ - *β* - hydroxypropylpiperazin - 1′ - yl) - 4 - phenylphthalazine hydrate, m.p. 89—90°C (yield 61%).
1 - (morpholin - 1′ - yl) - 4 - phenyl-phthalazine, m.p. 193—5°C (yield 39%).
1 - cyclopropylamino - 4 - phenylphthalazine, m.p. 195—6°C.
1 - cyclopentylamino - 4 - phenylphthalazine, m.p. 192—3°C.
1 - cyclopropylamino - 4 - *p* - chloro-phenylphthalazine, m.p. 190—2°C.
1 - cyclopropylamino - 4 - benzylphthalazine, m.p. 151—3°C.
1 - cyclohexylamino - 4 - phenylphthalazine, m.p. 300—3°C.
1 - (4′ - phenylpiperazin - 1′ - yl) - 4 - phenylphthalazine, m.p. 218—20°C.
1 - (4′ - *β* - hydroxyethylpiperazin - 1′ - yl) - 4 - phenyl - 7 - chlorophthalazine, m.p. 176—7°C.
1 - (4′ - *β* - hydroxyethylpiperazin - 1′ - yl) - 4 - (3′ - chloro - 4′ - methyl-phenyl) phthalazine, m.p. 140—2°C.
1 - (4′ - *β* - hydroxyethylpiperazin - 1′ - yl) - 4 - (2′ - methoxyphenyl)phthalazine hydrate, m.p. ca. 100°C.
1 - (4′ - *β* - hydroxyethylpiperazin - 1′ - yl) - 4 - (4′ - cyclophenyl)phthalazine, m.p. 221—2°C.
1 - (4′ - acetylpiperazin - 1′ - yl) - 4 - phenylphthalazine monohydrate, m.p. 125°C (with effervescence).
1 - (4′ - *β* - hydroxyethylpiperazin - 1′ - yl) - 4 - (4′ - methylthiophenyl) phthalazine, m.p. 162—3°C.
1 - (2′ - morpholinoethylamino) - 4 - phenyl-phthalazine, m.p. 138—9°C. (yield 50%).

1 - (4′ - β - hydroxyethylpiperazin - 1′ - yl) - 4 - (4′ - methoxyphenyl)phthalazine, m.p. 161—3°C (yield 69%).

1 - [4′ - (pyrrolidin - 1″ - yl) - piperidin - 1′ - yl] - 4 - phenylphthalazine, m.p. 157—8°C. (yield 35%).

1 - (4′ - methylpiperidin - 1 - yl) - 4 - phenylphthalazine, m.p. 143—4°C (yield 54%).

Example 8

To a stirred solution of 1 - [4′ - β - hydroxyethyl piperazin - 1′ - yl] - 4 - phenyl phthalazine (16.7 g.) in dry dioxan (250 ml.) was added slowly acetyl chloride (7.9 g.); after completion of the addition the mixture was heated under reflux for 2½ hours. The product was filtered cold and the solids (ca. 20.7 g. m.p. 234—7°) dissolved in water (100 ml.) and basified with aqueous sodium bicarbonate solution. The precipitated solids were extracted with chloroform and the combined extracts washed and dried ($MgSO_4$). The solvent was evaporated off to provide the crude acetate as a yellow solid m.p. 105—7°C (17 g. ca. 90%). Recrystallization from ethyl acetate/light petroleum (b.p. 40—60°C) provided 1 - [4′ - (2″ - acetoxyethyl)piperazin - 1′ - yl] - 4 - phenylphthalazine, m.p. 110—112°C.

Example 9

1 - (4′ - Ethoxycarbonylpiperazine - 1′ - yl) - 4 - phenyl phthalate (16.3 g.) was added to an aqueous alcoholic sodium hydroxide solution prepared by dissolving sodium hydroxide (5.5 g.) in water (5.5 ml.) and diluting with alcohol (50 ml.), and the mixture heated under reflux for two hours. The cold mixture was acidified with dilute acetic acid, concentrated to small volume and then treated with excess water. The product was filtered, and the filtrate basified with dilute ammonium hydroxide solution. The precipitate was filtered off, washed with water and dried to yield the crude amine. Recrystallisation from aqueous alcohol provided 1 - (piperazin - 1′ - yl) - 4 - phenylphthalazine monohydrate, m.p. 176—8°C.

Example 10

1 - (Piperazin - 1′ - yl) - 4 - phenylphthalazine monohydrate (10.7 g.) was dehydrated by azeotroping with chloroform in a water separator and after evaporation of the solvent, dry dimethylformamide (100 ml.) was added to the residual anhydrous amine followed by powdered anhydrous potassium carbonate (4.8 g. 2 equivs.). To the stirred suspensions at room temperature was added slowly methyl chloroacetate (4.15 g.) and then the mixture was heated on a steam bath with stirring for 1½ hours. The solvent was partially removed under reduced pressure, the product treated with excess water and was then extracted with chloroform. The solvent was evaporated off and the residual gum washed with light petroleum (b.p. 40—60°C). Recrystallisation from ethyl acetate/light petroleum (b.p. 40—60°C) gave fine needles of methyl[4′ - (4″ - phenylphthalazine - 1″ - yl)piperazin - 1′ - yl]acetate, m.p. 140—1°C. (6.8 g. 55%). Similarly the corresponding benzyl acetate was prepared as its monohydrate, m.p. 78—80°C (softens 73°C.)

Example 11

By the method of Example 10 using allyl bromide in place of methylchloroacetate, 1 - (4′ - allyl - 1′ - piperazinyl) - 4 - phenylphthalazine, m.p. 156—7°C. was obtained.

In the following examples of pharmaceutical compositions, the term "medicament" is used to indicate the compound 1 - (4′ - β - hydroxyethylpiperazin - 1′ - yl) - 4 - phenylphthalazine. That compound may of course be replaced in these compositions by any other compound of the invention and the amount of medicament may be increased or decreased as is well known in the art depending on the degree of activity of the medicament used.

Example 12

Tablet formulation

	mg/tablet
Medicament	15
Lactose	86
Maize Starch (dried)	45.5
Gelatin	2.5
Magnesium stearate	1.0

The medicament was powdered and passed through a B.S. No. 100 sieve and well mixed with the lactose and 30 mg. of the maize starch, both passed through a B.S. No. 44 sieve.

The mixed powders were massed with a warm gelatin solution prepared by stirring the gelatin in water and heating to form a 10% w/w solution. The mass was granulated by passing through a B.S. No. 12 sieve and the moist granules dried at 40°C.

The dried granules were re-granulated by passing through a B.S. No. 14 sieve and the balance of the starch sieved 44 mesh and the magnesium stearate sieved 60 mesh were added and thoroughly mixed.

The granules were compressed to produce tablets each weighing 150 mg.

Example 13

Tablet formulation

	mg/Tablet
Medicament	100
Lactose	39
Maize starch (dried)	80
Gelatin	4.0
Magnesium stearate	2.0

The method of preparation is identical with that of Example 12 except that 60 mg. of starch is used in the granulation process and 20 mg. during tabletting.

Example 14
Capsule formulation

	mg/Capsule
Medicament	250
Lactose	150

The medicament and lactose were passed through a No. 44 B.S. sieve and the powders well mixed together before filling into hard gelatin capsules of suitable size, so that each capsule contained 400 mg. of mixed powders.

Example 15
Suppositories

	mg/Suppository
Medicament	50
Oil of Theobroma	950

The medicament was powdered and passed through a B.S. No. 100 sieve and triturated with molten oil of Theobroma at 45°C to form a smooth suspension.

The mixture was well stirred and poured into moulds, each of nominal 1 G. capacity, to produce suppositories.

Example 16
Cachets

	mg/Cachet
Medicament	100
Lactose	400

The medicament was passed through a B.S. No. 40 mesh sieve, mixed with lactose previously sieved 44 mesh and filled into cachets of suitable size so that each contained 500 mg.

Example 17
Intramuscular Injection (Suspension in aqueous vehicle)

Medicament	10 mg.
Sodium Citrate	5.7 mg.
Sodium carboxymethylcellulose (low viscosity grade)	2.0 mg.
Methyl para-hydroxybenzoate	1.5 mg.
Propyl para-hydroxybenzoate	0.2 mg.
Water for Injection to	1.0 ml.

The sodium citrate and sodium carboxymethylcellulose were mixed with sufficient water for Injection at 80°C. The mixture was cooled to 50°C and the methyl and propyl parahydroxybenzoates added followed by the medicament previously milled and sieved 300 mesh. When cool the Injection was made up to volume and sterilized by heating in an autoclave.

WHAT WE CLAIM IS:—

1. Phthalazines having the general formula

and acid addition salts and quaternary ammonium derivatives thereof wherein

R represents aryl or aralkyl

R_1 and R_2, which may be the same or different, represent hydrogen; cycloalkyl; or cycloalkyl alkyl; provided that both R_1 and R_2 are not hydrogen; or

R_1 and R_2 separately represent the same or different heterocyclic or heterocyclic-alkyl or, together with the adjacent nitrogen, represent heterocyclic, the said heterocyclic groups being rings of 5 to 7 atoms at least one of which atoms is carbon, and at least one and optionally up to four of which atoms are hetero atoms selected from nitrogen, oxygen or sulphur; and

R_3 and R_4, which may be the same or different, represent hydrogen; halogen; cyano; hydroxy; nitro; amino; alkylamino; carboxy; carboxyamido; alkyl; alkylcarbonyl; alkoxy; alkoxycarbonyl; hydroxy alkyl; halogenoalkyl; or alkyl- or aryl-thio, -sulphinyl or -sulphonyl, the said heterocyclic rings being optionally substituted by alkyl; hydroxyalkyl; halogenoalkyl; aryl; aralkyl; carboxylalkyl; alkoxy- or aralkoxy-alkyl; alkoxy- or aralkoxy-carbonyl; alkoxy- or aralkoxy-carbonylalkyl; alkyl- or aryl-sulphonyloxyalkyl; aminoalkyl; alkylamino-alkyl; acyl; acyl- or acyloxy-alkyl; or by a further heterocyclic or heterocyclic-alkyl group, the heterocyclic rings of which have 5 to 7 atoms, one or two of which are hetero-atoms selected from nitrogen, oxygen or sulphur and the remainder of which ring atoms are carbon, which rings are themselves optionally substituted by alkyl, hydroxyalkyl or halogenoalkyl, the terms alkyl and aryl being as hereinbefore defined.

2. Phthalazines as claimed in Claim 1, wherein

R represents phenyl or phenyl-lower alkyl (the phenyl or phenyl moiety of which is optionally substituted by halogen; cyano; hydroxy; nitro; amino; lower alkylamino; lower alkyl; lower alkylcarbonyl; lower alkoxy; lower alkoxycarbonyl; hydroxy lower alkyl; halogeno lower alkyl; or lower alkylthio, -sulphinyl or -sulphonyl);

R_3 and R_4, which may be the same or different, represent hydrogen; halogen; cyano; hydroxy; nitro; amino; lower alkylamino; lower alkyl; lower alkylcarbonyl; lower alkoxy; lower alkoxycarbonyl; hydroxy

lower alkyl; halogeno lower alkyl; or lower alkyl-thio, -sulphinyl or -sulphonyl;

R_1 represents hydrogen;

R_2 represents cycloalkyl or cycloalkyl-lower alkyl (the cycloalkyl or cycloalkyl moiety of which has 3 to 6 carbons); or heterocyclic or heterocyclic-lower alkyl; or

R_1 and R_2, together with the adjacent nitrogen, represent a heterocyclic ring; the heterocyclic rings represented by R_2, or R_1 and R_2 together, having from 5 to 6 ring atoms, at least one of which is carbon and at least one, and optionally up to 4, of which atoms are hetero atoms selected from nitrogen, oxygen or sulphur, which heterocyclic rings are optionally substituted by lower alkyl; hydroxy- or halogeno-lower alkyl; phenyl; phenyl(lower) alkyl; carboxy(lower)alkyl; lower alkoxy- or phenyl(lower)alkoxy-lower alkyl; lower alkoxy-carbonyl or -carbonyl(lower) alkyl; lower alkyl- or phenyl-sulphonyloxy(lower) alkyl; amino(lower)alkyl; lower alkylamino-(lower)alkyl; lower acyl; lower alkylamino-acyloxy-lower alkyl; or by a further heterocyclic or heterocyclic-lower alkyl group, the further heterocyclic rings having from 5 to 6 ring atoms, one or two of which are hetero atoms selected from nitrogen, oxygen or sulphur and the remainder of which ring atoms are carbon, which further rings are optionally substituted by lower alkyl, hydroxy- or halogeno-lower alkyl, the phenyl substituents or the phenyl moiety of substituents on the aforementioned heterocyclic rings being optionally substituted by halogen, cyano, hydroxy, amino, lower alkylamino, lower alkyl or lower alkoxy.

3. Phthalazines as claimed in Claim 2, wherein

R_3 and R_4, which may be the same or different, represent hydrogen or halogen;

R represents phenyl or benzyl, the phenyl or phenyl moiety of which is optionally substituted by halogen, cyano, hydroxy, amino, alkylamino, alkyl, alkoxy or alkylthio (the alkyl or alkoxy moieties of which groups have 1 to 4 carbons); and either

R_1 represents hydrogen and R_2 represents cycloalkyl of 3 to 6 carbons, heterocyclic or heterocyclic-lower alkyl, or

R_1 and R_2, together with the adjacent nitrogen, represent a heterocyclic ring;

the heterocyclic rings of R_2, or R_1 and R_2 together, having from 5 to 6 ring atoms up to two of which are nitrogen, up to one of which is oxygen, and the remainder of which are carbon, which heterocyclic rings are optionally substituted by alkyl, hydroxyalkyl or halogenoalkyl of 1 to 4 carbons; phenyl or benzyl; methoxy- or ethoxy-carbonyl, -carbonmethyl or -carbonyl ethyl; acetyl, or propionyl; acetyl-, propionyl; acetyloxy- or propionyloxymethyl or -ethyl; or by a further heterocyclic or heterocyclicmethyl, ethyl, propyl or butyl, the further heterocyclic rings having from 5 to 6 ring atoms, up to two of which are nitrogen, up to one of which is oxygen and the remainder of which are carbon, which further rings are optionally substituted by alkyl, hydroxyalkyl or halogenoalkyl of 1 to 4 carbons, the phenyl substituents or the phenyl moiety of substituents on the heterocyclic rings being optionally substituted by halogen; hydroxy; methyl; ethyl; methoxy or ethoxy.

4. Phthalazines as claimed in Claim 3, wherein R_3 and R_4, which may be the same or different, represent hydrogen or chlorine; R represents phenyl or benzyl, the phenyl or phenyl moiety of which is optionally substituted by one or more of methyl, chlorine, cyano methoxy or methylthio; and either

R_1 represents hydrogen and R_2 represents cyclopropyl, cyclopentyl, cyclohexyl, 2 - morpholinoethyl or 3 - morpholinopropyl, or R_1 and R_2, together with the adjacent nitrogen, represent piperidin - 1 -yl, pyrolidin - 1 - yl, morpholin - 4 - yl, 4 - methylpiperidin - 1 - yl, 4 - β - hydroxyethylpiperidin - 1 - yl, 4 - (pyrrolidin - 1′ - yl)piperidin - 1 - yl, 4 - [1′ - (1″ - β - hydroxyethylpiperidin - 4″ - yl)prop - 3′ - yl]piperidin - 1 - yl, or a 4 - X substituted piperazin - 1 - yl group wherein X represents hydrogen, ethoxycarbonyl, methyl, allyl, β - hydroxyethyl, β - hydroxypropyl, phenyl, *o* - tolyl, acetyl, acetyloxyethyl, methoxycarbonylmethyl, acetylmethyl or benzyloxycarbonyl methyl.

5. 1 - (4′ - Methyl - 1′ - piperazinyl) - 4 - phenyl - phthalazine.

6. 1 - [4′ - (β″ - Hydroxyethyl)-piperazin - 1′ - yl] - 4 - phenylphthalazine.

7. 1 - (4′ - ethoxycarbonylpiperazin - 1′ - yl) - 4 - phenylphthalazine.

8. 1 - [(3′ - Morpholinopropyl)amino] - 4 - phenylphthalazine.

9. 1 - (4′ - β - Hydroxycthylpiperazine - 1′ - yl) - 4 - (*p* - chlorophenyl) phthalazine.

10. 1 - (Piperidin - 1′ - yl) - 4 - phenyl-phthalazine.

11. 1 - (Pyrrolidin - 1′ - yl) - 4 - phenyl-phthalazine.

12. 1 - (4′ - *o*. Tolylpiperazin - 1′ - yl) - 4 - phenylphthalazine.

13. 1 - [4′ - [1″ - (1‴ - β - Hydroxy-ethylpiperidin - 4‴ - yl)prop - 3″ - yl] - piperidin - 1′ - yl] - 4 - phenylphthalazine.

14. 1 - (4′ - β - Hydroxyethyl-piperidinyl) - 4 - phenylphthalazine.

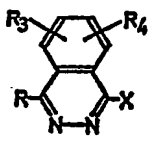
15. 1 - (4′ - β - Hydroxyethylpiperazin - 1′ - yl) - 4 - benzylphthalazine.

16. 1 - (4′ - β - Hydroxypropylpiperazin - 1′ - yl) - 4 - phenylphthalazine.

17. 1 - (Morpholin - 4′ - yl) - 4 - phenyl-phthalazine.

18. 1 - Cyclopropylamino - 4 - phenyl-phthalazine.

19. 1 - (4′ - β - Hydroxyethylpiperazin - 1′ - yl) - 4 - phenyl - 7 - chlorophthalazine.
20. 1 - (4′ - β - Hydroxyethylpiperazin - 1′ - yl) - 4 - (3′ - chloro - 4′ - methylphenyl)phthalazine.
21. 1 - (4′ - β - Hydroxyethylpiperazin - 1′ - yl) - 4 - (2′ - methoxyphenyl)-phthalazine.
22. 1 - (4′ - β - Hydroxyethylpiperazin - 1′ - yl) - 4 - (4′ - cyanophenyl)phthalazine.
23. 1 - (4′ - Acetylpiperazin - 1′ - yl) - 4 - phenylphthalazine.
24. 1 - (4′ - β - Hydroxyethylpiperazin - 1′ - yl) - 4 - (4′ - methylthiophenyl)-phthalazine.
25. 1 - (2′ - Morpholinoethylamino) - 4 - phenylthalazine.
26. 1 - (4′ - β - Hydroxyethylpiperazin - 1′ - yl) - 4 - (4′ - methoxyphenyl)phthalazine.
27. 1 - [4′ - (Pyrrolidin - 1′′ - yl)-piperidin - 1′ - yl] - 4 - phenylphthalazine.
28. 1 - (4′ - Methylpiperidin - 1 -yl) - 4 - phenylphthalazine.
29. 1 - (4′ - (2′′ - Acetoxyethyl)piperazin - 1′ - yl] - 4 - phenylphthalazine.
30. 1 - (Piperazin - 1′ - yl) - 4 - phenylphthalazine.
31. Methyl[4′ - (4′′ - phenylphthalazine - 1′′ - yl)piperazin - 1′ - yl]acetate.
32. Benzyl[4′ - (4′′ - phenylphthalazine - 1′′ - yl)piperazin - 1′ - yl]acetate.
33. 1 - (4′ - Allyl - 1′ - piperazinyl) - 4 - phenylphthalazine.
34. 1 - (4′ - Acetylmethylpiperazin - 1′ - yl) - 4 - phenylphthalazine.
35. Pharmaceutically acceptable acid addition salts and quaternary ammonium derivatives of any one of the compounds claimed in Claim 1.
36. Process for preparing a phthalazine as claimed in any one of Claims 1 to 35, which comprises reacting a compound of the formula:—



II

wherein R_2, R_3 and R_4 are as defined in Claim 1 and X represents halogen, or alkyl- or aryl-thio, -sulphinyl or -sulphonyl; with an amine, or an acid addition salt thereof, of the formula:—

HNR_1R_2 III

wherein R_1 and R_2 are as defined in Claim 1, and thereafter optionally converting by methods known *per se* a substituent of a resultant product to another substituent falling within the definitions of R, R_1, R_2, R_3 or R_4 given in Claim 1, the resultant compounds of formula 1 being isolated either *per se* or as acid addition salts or quaternary ammonium derivatives.
37. Process as claimed in Claim 36 wherein the reaction is carried out at elevated temperature.
38. Process as claimed in Claim 36 or Claim 37 wherein the reaction is carried out in a solvent and at the reflux temperature of the reaction mixture.
39. Process as claimed in Claim 38, wherein the solvent is selected from benzene, chloroform, toluene, acetone, dioxan, dimethylformamide, or dimethylsulphoxide.
40. Process for preparing a phthalazine derivative, substantially as described in any one of Examples 1 to 6 and 8 to 11.
41. Phthalazine derivative whenever prepared by a process as claimed in any one of Claims 36 to 40.
42. Pharmaceutcial compositions comprising as an active ingredient a phthalazine derivative as claimed in Claim 1 or a pharmaceutically acceptable acid addition salt or quaternary ammonium derivative thereof, in association with a pharmaceutically acceptable carrier therefor.
43. A composition as claimed in Claim 42 in the form of a tablet, capsule, suppository, solution or suspension.
44. A composition as claimed in Claim 42 in a dosage unit form containing from 1 to 1000 mg. of said active ingredient.
45. A composition as claimed in Claim 44 containing from 5 to 500 mg. of said active ingredient.
46. A composition as claimed in Claim 45 containing from 10 to 250 mg. of said active ingredient.
47. Pharmaceutical compositions substantially as described in any one of Examples 12 to 17.
48. A method of treating inflammation in non-human animals comprising administering to said animals an amount effective to reduce inflammation of a phthalazine compound as claimed in Claim 1 or a pharmaceutically acceptable acid addition salt or quaternary ammonium derivative thereof.

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